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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/726,571	12/04/2003	Hasan Khatib	011335.52842US	5115

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EXAMINER

CHO, DAN SUNG C

ART UNIT	PAPER NUMBER
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1634

DATE MAILED: 10/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/726,571

Applicant(s)

KHATIB, HASAN

Examiner

Dan-Sung C. Cho

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 September 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-29 is/are pending in the application.
- 4a) Of the above claim(s) 1-11 and 13-29 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 12 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>5/11/2004, 6/1/2004, 8/11/2006</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This action is in response to the papers filed on 9/18/2006. Currently, claims 1-29 are pending. Claims 1-11, 22-24, 26-27 have been withdrawn as drawn to non-elected subject matter. In addition, claims 13-21, 25, 28, 29 of elected Group II and the linking claims 24 and 27 have been withdrawn as drawn to non-elected combination of SNPs. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This restriction is made FINAL.

Election/Restrictions

2. Applicant's election with traverse of Group II, Claims 12-21, 25, 28 and 29 in the paper filed on 9/18/2006 is acknowledged. Claims 24 and 27 are linking claims for the elected Group II.

3. The examiner required an election of a SNP combination for Groups II. Because Groups II encompassed claims with multiple combinations the restriction requirement was required. For example, claim 13, reciting "wherein the identity of at least two positions of positions 164, 269, 284, 407 and 989 are determined", encompasses combinations of 164, 269; 164, 284; 164, 407; 164, 989; 269, 284; 269, 407; 269, 989; 284, 407; 284, 989; 407, 989; 164, 269, 284; 164, 269, 407; 164, 269, 989; 164, 284, 407; 164, 284, 989, etc. The restriction requirement stated that the combination can be all 5 sites or any one combination of a subset of the 5 sites with at least two positions. The following is the relevant section on Restriction requirement for Groups II and III in the Office Action dated 8/17/2006:

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For Group II and Group III where the claims are drawn to a combination of SNPs a restriction is applied. As provided in MPEP 803.04, "Applicants will be required to select one combination for examination." The selected combination will be searched and examined. A combination may be as few as a SNP or as many SNP as the combination of all the recited polymorphic sites. Applicant is required to specifically indicate the single combination desired. All combinations containing the allowable combination of SNPs and any patentably indistinct combinations will be rejoined.

4. Claims 1-11, 22-24, 26-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic claim. The applicant elected all the SNPs at position 164 as the combination and no other position in the paper filed on 9/18/2006. Claims 13-21, 25, 28, 29 of elected Group II and the linking claims 24 and 27 encompass methods that require either haplotype (5 positions) or at least two positions. Therefore, claim 12 is the only elected claim and will be examined in this office action. The response traverses the restriction. The response asserts there is no justification for requiring selection of a combination. This argument has been reviewed. The restriction sets forth each SNP is different. A search for SNP 164 is not co-extensive of SNP269. Each SNP requires a text search for the specific mutation. Each position is patentably distinct and has different diagnostic uses. The response points to 803.4 which permits "up to 10" sequences to be examined. The MPEP does not say 10 sequences will be examined. The recitation "up to 10" encompasses 1. Each SNP sequence and each haplotype constitute independent and distinct inventions because they have different design and different functions. Thus for reasons above this restriction is made FINAL.

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5. Because of the explanation above the requirement is still deemed proper and is therefore made FINAL. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

7. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention and breadth of claims

8. Claim 12 is drawn to a method of SNP detection for bovine PI position 164. The invention is in a class of invention which the CAFC has characterized as “the

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unpredictable arts such as chemistry and biology.” *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

9. The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (*Genetics in Medicine*. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

10. Beauchemin et al. teaches that an evaluation of bovine DNA polymorphisms involving bovine growth hormone does not predict bovine growth and carcass characteristics (Beauchemin et al., 2006, *Genetics and Molecular Research*, 5:438-447; p 435, lines 2-4). When 430 animals were analyzed for two SNPs and two RFLP polymorphisms, none of the genotype was a significant source of bovine growth and carcass characteristics including an Msp-I RFLP (p 443, line 10). In addition DNA polymorphisms discovered in Bos taurus cattle may not be applicable to Bos indicus cattle (p444, lines 2-3).

11. Additionally, Ioannidis (*Nature Genetics*, Vol. 29, pages 306-309, November

2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

12. The art teaches that presence of SNPs in the same gene does not indicate that each of the genes is associated with the same diseases. Meyer et al. (PG Pub 2003/0092019), for example, teaches that SNPs in the CADPKL gene are not each associated with neuropsychiatric disorders such as schizophrenia. Specifically Meyer teaches that cadpk15 and cadpk16 are not associated with the disease, however cadpk17 has a p-value of less than 0.05, therefore an association exists. Each of these polymorphisms are SNPs within the CADPKL gene, however, it is apparent that they are not all associated in the same manner with disease. Thus, Meyer exemplifies that the association of a single SNP in a gene does not indicate that all SNPs within the gene are associated with the disease.

Guidance in the Specification.

13. The specification provides no evidence that the SNP at position 164 of bovine PI can be used for milk production trait association or any other use. The specification teaches haplotypes and their use in association study for bovine milk production but not any specific use of bovine PI genotype at position 164. The specification teaches PI haplotype with direct phased genotype data for positions 164, 269, 284, 407 and 989 and milk trait association (Tables 3 to 5); however, the direct association of the genotype at position 164 of bovine PI and milk production trait or any other trait or use is not disclosed. The specification does not enable any person skilled in the art to which it

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pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. While the position 164 of bovine PI can be detected with direct sequencing as disclosed in the specification, the applicant fails to provide enablement for use of the method of detecting SNPs at position 164 of bovine PI.

14. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses how to genotype bovine PI 164 SNPs but not how to use any SNP method. The specification teaches how to detect SNP at 164 but does not teach the skilled artisan to use the analysis. For example, if the skilled artisan determines a cow has an A at 164, it is unclear how the skilled artisan would use this information.

Working Examples

15. The specification has no working examples of any bovine PI genotype at position 164 use; the specification only discloses the use for the PI haplotype or 5 genotype combinations. The specification analyses only 164 in combination with 4 other markers to get a haplotype.

Quantity of Experimentation

16. The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied. Whether the method of SNP detection at bovine PI position 164 can be used for any traits or other use will require studying any potential use or traits that may be associated with the SNP. Freedman et al. teaches that previously reported BRCA2 SNPs with positive breast cancer association, the HH genotype of the N372H polymorphism and the M784V

polymorphisms, had no positive associations with breast cancer in their study of more than 4,200 cases (p 2438, left column, paragraph 1), possibly because of ethnic background difference. However, Freedman et al. found instead reports positive associations with cosegregating haplotypes in blocks1-3, the ancestrally related haplotypes 3d, 3f and 3i, and multiple SNPs that resided on this haplotype pattern (p 2438, left column, paragraph 2). Therefore the skilled artisan needs to determine multiple SNPs along with bovine PI SNP164, determine haplotypes and their association with milk production among different cattle populations (Bos taurus vs not Bos indicus).

17. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

18. The level of skill in the art is deemed to be high.

Conclusion

19. In the instant case, as discussed above, in a highly unpredictable art where the SNP and its association with phenotypic traits or other use is not disclosed in the specification. Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large

quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

20. Claim 12 is rejected under 35 U.S.C. 102(a) as being anticipated by IBISS (IBISS, The Interactive Bovine In Silico SNP database, CSIRO, Hawken, R, Barris W. and Dalrymple B. Pileup alignment dated July, 21, 2003, URL: <http://livestockgenomics.csiro.au/IBISS3/msff/btcn3197.txt>). IBISS teaches a total of 48,565 bovine SNPs of which 17,344 SNP are represented in more than one sequence and of which 3,372 SNPs have amino acid changes that are represented in more than one sequence. One of the bovine SNP entries identified by IBISS on July 21, 2003 is btcn3197 which is for Bos taurus serine (or cysteine) proteinase inhibitor, clade A (alpha-1antiproteinase, antitrypsin), member 1 (SERPINA1), mRNA or proteinase inhibitor (PI) (URL: <http://livestockgenomics.csiro.au/IBISS3/msff/btcn3197.txt>). Btcn3197 is the bovine PI sequence with extra nucleotide sequences upstream of position 1 of SEQ ID NO:1 of the instant application.

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Conclusion

21. **No claims allowable over the art.**

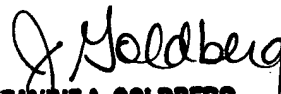
22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Dan-Sung C. Cho whose telephone number is (571) 272-9933. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

23. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

24. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). The Central Fax Number for official correspondence is (571) 273-8300.



Dan-Sung C. Cho
Examiner
AU1634
October 11, 2006


JEANNE A. GOLDBERG
PRIMARY EXAMINER
10/13/06